An amino alcohol ligand and its use in preparation of chiral proparglic tertiary alcohols and tertiary amines *via* enantioselective addition reaction

Technical Field

The invention relates to a process of asymmetric alkynylation of ketone or ketimine, involving the enantioselective addition of terminal alkynes to a trifluoromethyl ketone or ketimine intermediate to give a chiral tertiary proparglic alcohols or amines. The adduct compounds are the key precursors to the potent HIV reverse transcriptase inhibitor Efavirenz (DMP 266), DPC 961 and DPC 083. The invention also relates the new amino alcohol ligand used in the above process.

Background Art

Human immunodeficiency virus (HIV) is prone to mutation, which leads to drug resistance. It is known that some compounds are reverse transcriptase inhibitors and are effective agents in the treatment of HIV, and similar diseases, e.g. azidothymidine or AZT. DPC083 , DPC 961 and Efavirenz (Sustiva ^{TM}) are second generation HIV non-nucleoside reverse transcriptase inhibitors(NNRTIs) with enhanced potency. Efavirenz (Sustiva ^{TM}) has approved for the treatment of HIV (*Antimicrob. Agents Chemother.* **1995**, 39, 2602). DPC083 and DPC 961 are currently undergoing clinical evaluation (*Journal of Medicinal Chemistry* vol.43, no.10, **2000**, 2019-2030).

Some methods have been reported for the synthesis of Efavirenz (Sustiva ^{TM}) (Angew. Chem. Int. Ed. no. 5, **1999**, 711-713; Journal of Organic Chemistry vol.63, no.23, **1998,** 8536-8543), DPC083 and DPC 961. These prior methods prepared DPC 961 by a fractional crystallization or 1,4-diastereoselective addition protocol , both employing auxiliary (*Journal of Organic Chemistry* vol.68, no.3, **2003**, 754-761; *Tetrahedron Letter* vol.41, **2000**, 3015-3019). Very recently, *WO***0170707** disclosed an asymmetric processe for preparing DPC961 via chiral ligand mediated asymmetric addition. However, in this process large excess strong base (lithium alkyl and LHMDS) and excess chiral ligand was used under very strict condition (-20°C).

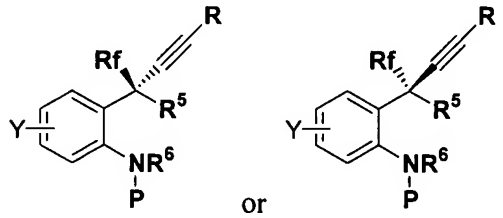
Disclosure of the invention

The present invention relates to a new process of asymmetric alkynylation of ketone or ketimine. The invention also provide the new amino alcohol ligand used in the alkynylation process.

A new process of asymmetric alkynylation of ketone or ketimine is disclosed, involving the enantioselective addition of terminal alkynes to a trifluoromethyl ketone or ketimine intermediate to give a chiral tertiary proparglic alcohols or amines. The adduct compounds are the key precursors to the potent HIV reverse transcriptase inhibitor Efavirenz (DMP 266), DPC 961 and DPC 083 . This was achieved by direct installation of the quaternary carbon atom of Efavirenz (Sustiva ^{TM}) , DPC083 and DPC 961 with absolute stereo controlling by chiral addition of zinc or copper acetylide to a ketone or ketimine intermediate to give a proparglic alcohol or amine, with enantiomeric excess up to 99%.

Further, it is unexpected that reaction of zinc or copper acetylide with a trifluoromethyl ketone or ketimine produces an optically active product. In the present invention, this is achieved with a new chiral amino alcohol to mediate the addition reaction along an asymmetric pathway. The unusually high levels of optical activity (up to 99% ee) and very mild reaction condition make the method advantageous and practical. The chiral ligand can also be recycled.

In this invention, there is disclosed a process which uses an amino alcohol ligand as catalyst for the asymmetric synthesis of the chiral compound of the structure

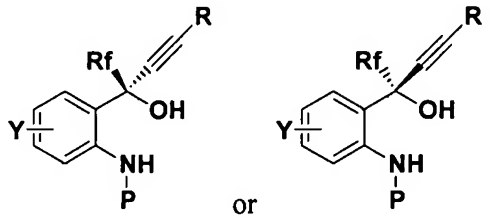


where Y is H, mono or multisubsubstituted electronwithdrawing group or electron-donating group, preferred is H, mono or di-subsubstituted electronwithdrawing group or electron -donating group, wherein Y can be located at *m*-,*o*-,or *p*-position of the benzene ring; More preferably, Y is H, Cl, Br, CH_3SO_2, $CH_3CH_2SO_2$, NO_2 or F. Most preferably, Y is F, Cl, Br;
P is hydrogen or an amino protecting group;

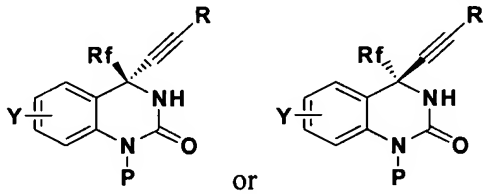
Rf is fluoro-containing alkyl, preferred is $C_1 \sim C_{20}$ fluoro-containing alkyl, more preferred is $C_1 \sim C_4$ fluoro-containing alkyl;

R is trialkylsilyl, alkyl, cycloalkyl or aryl group;

R^6 is hydrogen when R^5 is hydroxy, of the structure:

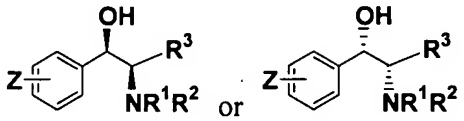


Also $R^5$and R^6 can be cyclization such as –HNCO- of the structure



where Y, P, R, Rf is the same as above.

The above amino alcohol ligand is of the structure



wherein R^1, R^2 is amino protecting group, R^1, R^2 is the same or different group,

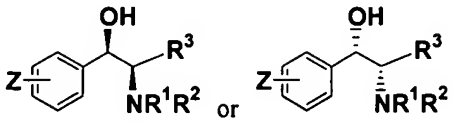
R^3 is alkyl, substituted alkyl (substituted group can be alkyloxy or silyoxy, especially), carboxylic group, carbalkoxy group, hydroxy methyl, cycloalkyl, aryl or CH_2OR^4; wherein R^4 is an oxygen protecting group,

Z is H, mono or multisubstituted electronwithdrawing group or electron-donating group, preferred is H, mono or di-subsubstituted electronwithdrawing group or electron -donating group, wherein Z can be located at *m*-,*o*-,or *p*-positon of the benzene ring; More preferable is H, F, Cl, Br, I, CH_3SO_2 OH, $PhCH_2O$, AcO, MeO, EtO, $Me_2NCH_2CH_2O$, $Et_2NCH_2CH_2O$, $PhCH_2OCO$, *t*-Bu, *i*-Pr, NH_2, or NO_2;

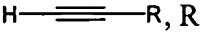
The process Comprising the steps of:

(a) providing a mixture of chiral ligand (1R, 2R)-2-*N*,*N*-substituted-1-(substituted

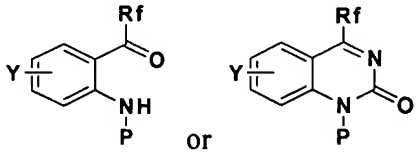
-phenyl)-2-R^3-substituted-2-aminoethanol or its enantiomer, of the structure



wherein R^1, R^2 , R^3 , Z is the same as above;

with a terminal alkyne and a Zn(II) , Cu(II) or Cu(I) salts in the presence of an organic base in organic solvent, wherein the terminal alkyne is  , R is the same as above.

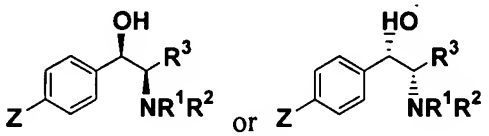
(b) mixing with the mixture of step (a) of reactant of the structure



wherein P, Rf, Y is the same as above;

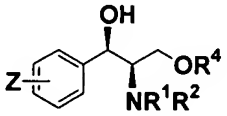
In an preferred embodiment, quenching the above reaction by adding a proton source , to give the desired compound. Preferable proton source is NH_4Cl aqueous (sat.), water, hydrochloric acid or citric acid aqueous.

In an embodiment, the amino alcohol ligand is a compound of the structure



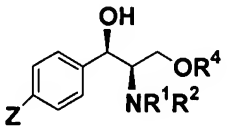
wherein R^1, R^2 ,R^3, Z is the same as above.

In another embodiment, the chiral ligand is a compound of the structure or its enatiomer



wherein R^1, R^2 ,R^4, Z is the same as above.

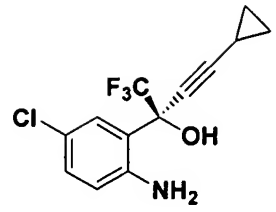
In another embodiment, the chiral ligand is a compound of the structure or its enatiomer



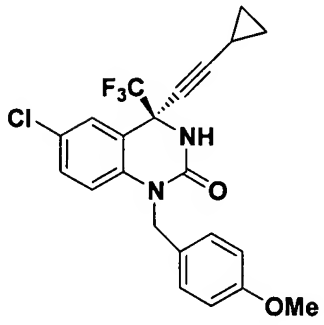
wherein R^1, R^2 ,R^4, Z is the same as above.

In an embodiment, this invention provides a novel process for making a compound of

the structure or its enatiomer

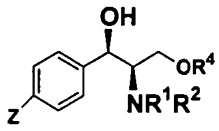


or of the structure or its enatiomer

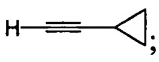


Comprising the steps of:

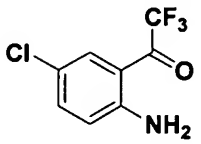
(a) providing a mixture of 0.1~3 molar equivalent of a chiral ligand (1R, 2R)-2-*N*,*N*-substitutedamino-1-(4-substituted-phenyl)-3-*O*-substituted-propane-1-ol, of the structure or its enatiomer,



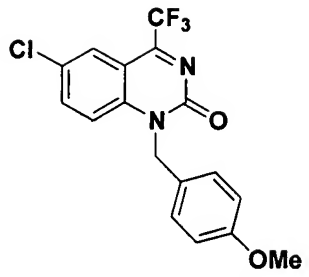
wherein Z, R^1,R^2, R^4 is the same as above,

with 0.1~3 molar equivalent of a terminal alkyne and 0.1~3 molar equivalent of Zn(II), Cu(I)or Cu(II) salts in the presence of 1~4 molar equivalent of an organic base in organic solvent, the terminal alkyne is  ;

(b) mixing with the mixture of step (a) of 1.0 molar equivalent of reactant of the structure



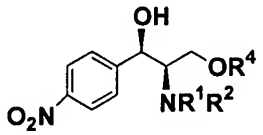
or of the structure that is the 4-methoxybenzyl protected ketimine(I):



(I)

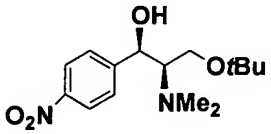
preferably, maintaining the resulting reaction mixture at a temperature of between about 0-50°C, especially at room temperature for 1-20hr; quenching by adding a proton source to give the desired compound.

In another embodiment, the chiral ligand is a compound of the structure or its enatiomer



wherein R^1, R^2, R^4 is the same as above; preferrably ,R^1, R^2 is Me.

In another preferred embodiment, the chiral ligand is a compound of the structure or its enatiomer



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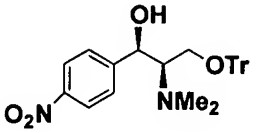


In another embodiment, wherein the stoichiometric ratios are about 0.1- 3 equivalent molar

of ligand to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 0.5- 3 equivalent molar of ligand to substrate ketone or ketimine.

In another preferred embodiment, wherein the stoichiometric ratios are about 1.2-1.5 equivalent molar of ligand to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 0.1- 3 equivalent molar of terminal alkyne to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 0.5- 3 equivalent molar of terminal alkyne to substrate ketone or ketimine.

In another preferred embodiment, wherein the stoichiometric ratios are about 1.2-1.5 equivalent molar of terminal alkyne to substrate ketone or ketimine.

In another embodiment, the metal salts is selected from $ZnCl_2$, $ZnBr_2$, ZnF_2, ZnI_2, $Zn(OTf)_2$, $Zn(SO_3CF_2H)_2$, $CuCl_2$, $CuBr_2$, $Cu(OTf)_2$, CuCl, CuBr, Cu(OTf), CuI.

In another preferred embodiment, the Zinc(II) or Cu(II) salts is $Zn(OTf)_2$ or $Cu(OTf)_2$.

In another preferred embodiment, the Zinc(II) is $Zn(OTf)_2$.

In another embodiment, wherein the stoichiometric ratios are about 0.1-3 equivalent molar of the Zinc(II) salt or Cu salt to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 0.5-3 equivalent molar of the Zinc(II) salt or Cu salt to substrate ketone or ketimine.

In another preferred embodiment, wherein the stoichiometric ratios are about 1.2-1.5 equivalent molar of the Zinc salt or Cu salt to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 1.0-4.0 equivalent molar of the organic base to substrate ketone or ketimine.

In another embodiment, wherein the stoichiometric ratios are about 2.0~3.5 equivalent molar of the organic base to substrate ketone or ketimine.

In another embodiment, wherein the organic base is selected from $MeN(iPr)_2$, $HNEt_2$, $N(iPr)_3$, pyridine, NEt_3, piperidine, NBu_3, $EtN(iPr)_2$.

In another preferred embodiment, wherein the organic base is NEt_3.

In another embodiment, the reaction is carried out in aprotic solvent or ethereal solvent.

Examples of aprotic solvent include THF, dioxane, CH_2Cl_2 Et_2O, benzene, DME, toluene, *n*-hexane, and cyclohexane, or mixture thereof.

In another preferred embodiment, solvent is toluene.

In another embodiment, wherein the reaction temperature is between about 0 °C and about 100 °C.

In another preferred embodiment, wherein the reaction temperature is between about 0°C and about 50 °C, especially at room temperature.

In another embodiment, wherein R^1 and R^2 is alkyl, substituted alkyl, benzyl or substituted benzyl or trialkysily protected groups, the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, C_1~C_3 hydroxy alkyl, C_1~C_4 alkyl, C_1~C_3 alkoxy, CN; or R^1, R^2 can be $-(CH_2)_nX(CH_2)_m-$, where X can be CH_2, O or NH;; n,m is an integer from 1 to 6.

P is hydrogen, alkyl, substituted alkyl, benzyl or substituted benzyl or trialkylsilyl protected groups, the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, C_1~C_3 hydroxyalkyl, C_1~C_4 alkyl, C_1~C_3 alkoxy, CN;

R^4 is alkyl, substituted alkyl, benzyl or substituted benzyl or trialkylsilyl, the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, C_1~C_3 hydroxy alkyl, C_1~C_4 alkyl, C_1~C_3 alkoxy, CN;

electronwithdrawing group is halogen, NO_2, CF_3, CH_3SO_2, $CH_3CH_2SO_2$, $PhCH_2OCO$,or AcO. electron-donating group is alkoxy (especially C_1~C_3 alkoxy), OH, $Me_2NCH_2CH_2O$, $Et_2NCH_2CH_2O$, NH_2, alkyl (especially C_1~C_4 alkyl).

In another preferred embodiment, wherein R^1 and R^2 is C_1~C_{20} alkyl , C_1~C_{20} substituted alkyl , benzyl, substituted benzyl or C_1~C_{20} trialkylsilyl protected groups, the substituted group is the same as above; or R^1, R^2 can be $-(CH_2)_nX(CH_2)_m-$, where X can be CH_2, O or NH; n,m is an integer from 1 to 6.

P is hydrogen, C_1~C_{20} alkyl, C_1~C_{20} substituted alkyl, benzyl or substituted benzyl or C_1~C_{20} trialkylsilyl protected groups, the substituted group is the same as above;

R is C_1~C_{20} trialkylsilyl, C_1~C_{20} alkyl, C_3~C_{20} cycloalkyl or aryl, the aryl is phene, naphthalene, furan, thiophene, pyrrole.

R^3 is $C_1 \sim C_{20}$ alkyl; $C_1 \sim C_{20}$ alkyl substituted with alkyloxy or silyoxy, carboxylic group, $C_1 \sim C_{20}$ carbalkoxy group, hydroxyl methyl, $C_3 \sim C_{20}$ cycloalkyl , aryl or CH_2OR^4, wherein R^4 is $C_1 \sim C_{20}$ alkyl , $C_1 \sim C_{20}$ substituted alkyl, benzyl or substituted benzyl or $C_1 \sim C_{20}$ trialkylsilyl, the substituted group is the same as above.

Z is H, F, Cl, Br, I, CH_3SO_2 OH, $PhCH_2O$, AcO, MeO, EtO, $Me_2NCH_2CH_2O$, $Et_2NCH_2CH_2O$, $PhCH_2OCO$, *t*-Bu, *i*-Pr, NH_2, or NO_2;

Y is H, F, Cl, Br, I, CH_3SO_2 OH, $PhCH_2O$, AcO, MeO, EtO, $Me_2NCH_2CH_2O$, $Et_2NCH_2CH_2O$, $PhCH_2OCO$, *t*-Bu, *i*-Pr, NH_2, or NO_2;

In another preferred embodiment, wherein R^1 and R^2 is C_1~C_4 alkyl , tri-phenyl methyl, *t*-butyldimethylsilyl， benzyl unsubstituted or substituted with C_1-C_4 alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or N-trialkylsilyl groups; or R^1, R^2 can be $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_2N(CH_2)_2-$, $-(CH_2)_5-$ or $-(CH_2)_6-$.

P is hydrogen, C_1~C_4 alkyl , tri-phenyl methyl, *t*-butyldimethylsilyl， benzyl unsubstituted or substituted with C_1~C_4 alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl;

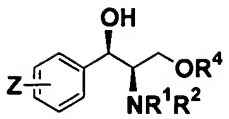
R is C_1~C_4 alkyl, C_3~C_6 cycloalkyl or aryl, the aryl is phene, naphthalene, furan, thiophene, pyrrole.

R^3 is C_1~C_4 alkyl; C_1~C_4 alkyl substituted with alkyloxy or silyoxy, carboxylic group, C_1~C_4 carbalkoxy group, hydroxyl methyl, $C_3 \sim C_6$ cycloalkyl , aryl or CH_2OR^4, wherein R^4 is C_1~C_4 alkyl , tri-phenyl methyl, *t*-butyldimethylsilyl， benzyl unsubstituted or substituted with C_1~C_4 alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl;

Y is H, Cl, Br, CH_3SO_2、$CH_3CH_2SO_2$、NO_2 or F;

Halogen or halo is fluoro, chloro, bromo and iodo.

In this invention, there is also disclosed a novel chiral ligand of the structure or its enatiomer



wherein R^1, R^2 is amino protecting group, R^1, R^2 is the same or different group,

R^4 is oxygen protecting group,

Z is mono or multisubstituted electronwithdrawing group or electron-donating group, wherein Z can be located at *m*-,*o*-,or *p*-positon of the benzene ring.

Preferably, R^1 and R^2 is alkyl, substituted alkyl, benzyl, substituted benzyl, or trialkylsilyl group; or R^1, R^2 can be $-(CH_2)_nX(CH_2)_m-$, where X can be CH_2, O or NH;; n,m is an integer from 1 to 6.

R^4 is alkyl, substituted alkyl, benzyl, substituted benzyl, or trialkylsilyl group; Example of the substituted group of alkyl or benzyl is phenyl , naphthyl, halogen, hydroxy, NO_2, $C_1 \sim C_3$ alkoxy, CN;

Z is halogen, NO_2, CF_3, CH_3SO_2, $CH_3CH_2SO_2$, CH_3O, OH or alkyl;

Preferably, Z is mono or multisubstituted electronwithdrawing group or electron-donating group, more preferably Z is F, Cl, Br, I, CH_3SO_2 OH, $PhCH_2O$, AcO, MeO, EtO, $Me_2NCH_2CH_2O$, $Et_2NCH_2CH_2O$, $PhCH_2OCO$, *t*-Bu, *i*-Pr, NH_2, or NO_2

More preferably, R^1 ,R^2 is $C_1 \sim C_{20}$ alkyl, C_1-C_{20} substituted alkyl, benzyl ,substituted benzyl, C_1-C_{20} trialkylsilyl group; or R^1, R^2 can be $-(CH_2)_nX(CH_2)_m-$, where X can be CH_2, O or NH; n,m is an integer from 1 to 6.

R^4 is C_1-C_{20} alkyl, C_1-C_{20} substituted alkyl, benzyl, substituted benzyl, or C_1-C_{20} trialkylsilyl group ;

Most Preferably, R^1 ,R^2 is C_1-C_4 alkyl(such as methyl), benzyl unsubstituted or substituted with C_1-C_4 alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or trialkylsilyl group; or R^1, R^2 can be $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_2N(CH_2)_2-$, $-(CH_2)_5-$ or $-(CH_2)_6-$.

R^4 is C_1-C_4 alkyl (such as butyl), benzyl unsubstituted or substituted with C_1-C_4 alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or trialkylsilyl group which exclude *t*-Butyldimethylsilyl.

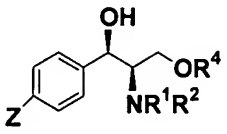
Z is Cl, Br, NO_2, CF_3, CH_3SO_2, $CH_3CH_2SO_2$, CH_3O, OH or $C_1 \sim C_4$ alkyl, especially Z is CH_3SO_2 or NO_2;

and when Z is NO_2 at 4-postion of the phenyl, R^1 is $N{=}O$, R^2 is $COCH_3$, R^4 is only alkyl, substituted alkyl, benzyl ,substituted benzyl, or trialkylsilyl;

and when Z is NO_2 at 4-postion of the phenyl, R^1, R^2 is CH_3, the ligand is only (1R, 2R)-2-*N*,*N*-dimethylamino-1-(4- nitrophenyl)-3-*O*-R^4-1-ol;

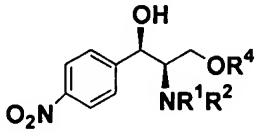
and when Z is OCH_3 at 4-postion of the phenyl, R^1, R^2 is CH_3, R^4 is only alkyl, substituted alkyl, benzyl ,substituted benzyl; said substituted group is the same as above;

In another embodiment, the novel chiral ligand is a compound of the structure or its enatiomer



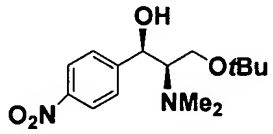
R^1, R^2, R^4, Z is the same as above.

In another embodiment, the novel chiral ligand is a compound of the structure or its enatiomer



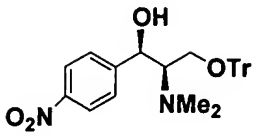
R^1, R^2, R^4 is the same as above, preferably , R^1, R^2 is Me.

In another preferred embodiment, the novel chiral ligand is a compound of the structure or its enatiomer



In another preferred embodiment, the novel chiral ligand is a compound of the structure or its enatiomer

In another preferred embodiment, the novel chiral ligand is a compound of the structure or its enatiomer



As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; if the number of carbon atoms is unspecified, "alkyl" is intended to include 1 to 20 carbon atoms, preferred is 1 to 4 carbon atoms, both branched and straight-chain saturated aliphatic hydrocarbon groups. For example, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl.

"Halogen" or "halo" as used herein, means fluoro, chloro, bromo and iodo.

"alkoxyl" is intended to include both branched- and straight-chain groups having the specified number of carbon atoms; if the number of carbon atoms is unspecified, "alkoxyl" is intended to include 1 to 20 carbon atoms, preferred is 1 to 4 carbon atoms.

If the number of carbon atoms is unspecified, "cycloalkyl" is intended to include 3 to 20 carbon atoms, preferred is 3 to 6 carbon atoms.

"aryl" is intended to include phenyl, naphenyl, furan, thiophene , pyrrole, preferred is phenyl.

"carbalkoxy group" is intended to include 1 to 20 carbon atoms, preferred is 1 to 4 carbon

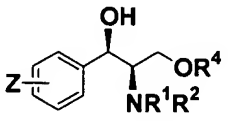
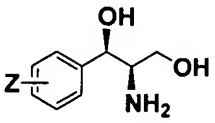
In the processes of this present invention, R^1 and R^2 is the same or different group. R^1 and R^2 is any suitable amino protecting group, and includes, but is not limited to, alkyl , substituted alkyl (the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, C_1~C_3 hydroxy, alkyl, C_1~C_3 alkoxy, CN), benzyl, substituted benzyl(the substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, C_1~C_3 hydroxy, alkyl, C_1~C_3 alkoxy) or trialkylsilyl, or R^1, R^2 can be $-(CH_2)_nX(CH_2)_m-$, where X can be CH_2, O or NH;; n,m is an integer from 1 to 6. Examples of R^1 or R^2 is C_1~C_4 alkyl, tri-phenyl methyl, *t*-butyldimethylsilyl, benzyl unsubstituted or substituted with C_1-C_{20} alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl;

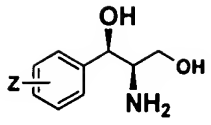
para-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; preferred is C_1-C_4 alkyl, benzyl unsubstituted or substituted with C_1-C_4 alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or R^1, R^2 can be $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_2N(CH_2)_2-$, $-(CH_2)_5-$ or $-(CH_2)_6-$. Other protective groups are according to T. W. Greene *et al.*, Protective groups in Organic Synthesis 3rd Ed. John Wiley 1999, pp. 494-653. A preferable amino protecting group is *para*-methoxybenzyl.

P is hydrogen or any suitable amino protecting group described as above.

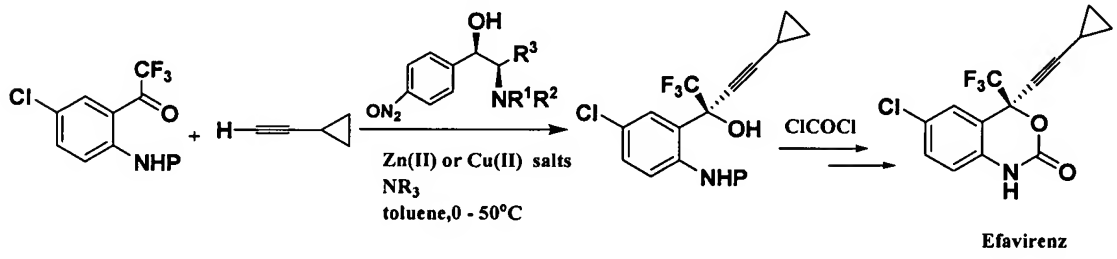
In the processes of this present invention, R^4 is any suitable oxygen protecting group, and includes, but is not limited to, alkyl , substituted alkyl, benzyl or substituted benzyl or trialkylsilyl protected groups. Preferred is C_1~C_{20} alkyl unsubstituted or substituted, benzyl unsubstituted or substituted, or trialkylsilyl protected groups. The substituted group can be phenyl, naphenyl, halo, nitro, hydroxy, C_1~C_3 hydroxyalkyl, C_1~C_3 alkoxy, CN. Examples of R^3 is C_1~C_4 alkyl , tri-phenyl methyl, *t*-butyldimethylsilyl, benzyl unsubstituted or substituted with C_1-C_4 alkyl; *para*-methoxy benzyl; *para*-nitrobenzyl; *para*-chlorobenzyl; 2, 4-dichlorobenzyl; 2, 4-dimethoxybenzyl; or trialkylsilyl groups. Other protective groups are according to T. W. Greene *et al.*, Protective groups in Organic Synthesis 3rd Ed. John Wiley 1999, pp. 17-245. A preferable oxygen protecting group is *t*-butyl.

In the processes of this present invention, electronwithdrawing group includes, but is not limited to, halogen, NO_2, CF_3, CH_3SO_2, $CH_3CH_2SO_2$,$PhCH_2OCO$ or AcO. Electron-donating group includes, but is not limited to, alkoxy especialy C_1~C_{20} alkoxy, OH, $Me_2NCH_2CH_2O$, $Et_2NCH_2CH_2O$, NH_2, alkyl.

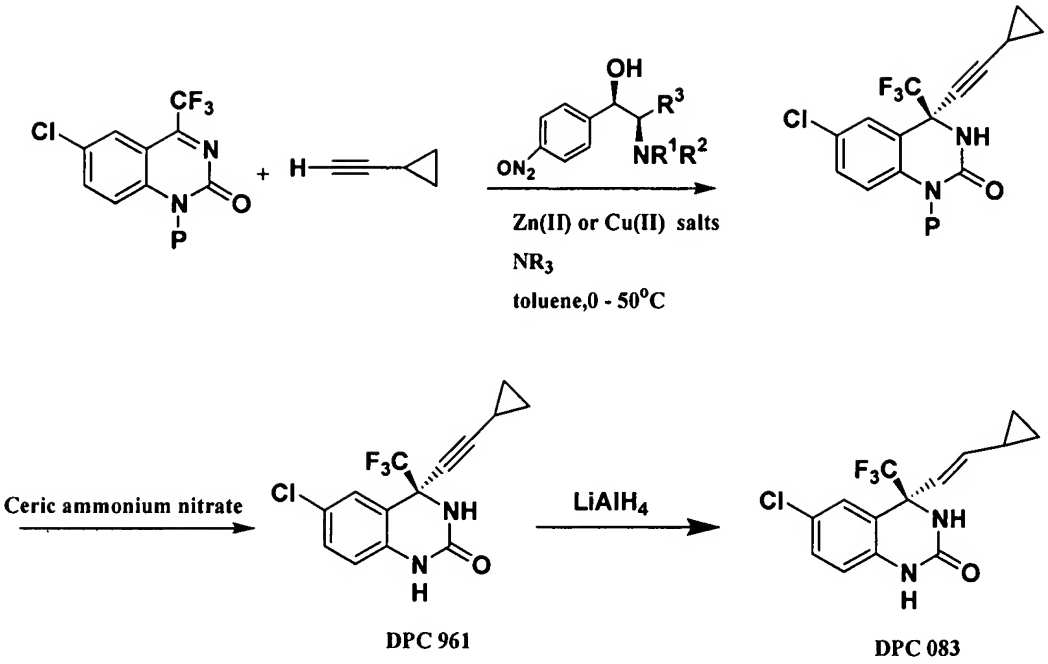
The synthesis of the chiral ligand  or its enantiomer is based on the simple and short modification of  or its enantiomer. The hygroxy group at 3-position and amino at 2-position group was protected according to T. W. Greene *et al.*, Protective groups in Organic Synthesis 3rd Ed. John Wiley 1999.

For example, the amino group at 2-position of  can be protected first by condensation of corresponding aldehyde then by reducing in organic solvent. Example of the reductant can be formic acid, $NaBH_4$, KBH_4, $LiAlH_4$ or Pd/C. The amino group at 2-position also can be protected by reaction with R^1X or R^2X in organic solvent in the presence of base, wherein X is halogen. The hygroxy group at 3-position can be protected with *t*-butyl by reaction with iso-butene catalydzed by acid. The hygroxy group at 3-position also can be protected with R^3 by reaction with R^3X, wherein X is halogen..The above reaction condition can be routine. Said base can be inorganic base or organic base, for example , K_2CO_3, Na_2CO_3, NaOH, KOH or NEt_3. Example of said organic solvent can be alcohol, alkyl substituted by halogen or ether. Example of the protection detail is refluxing with formaldehyde and formic acid to protect amino group with di-methyl, or reacting with benzaldehyde for condensation and then reducing by $NaBH_4$ to protect the amino group by benzyl group.

Efavirenz, DPC 961 and DPC 083 can be synthesized by the following method.



Efavirenz



The present invention provided a novel ligand.The use of the ligand relates to asymmetric addition particularly to .a direct synthesis of the optically active DPC 961 , DPC083 and efavirenz, by chiral addition of zinc or copper acetylide to a ketimine intermediate to give a proparglic amine, with enantiomeric excess up to 99%; or by chiral addition of zinc or copper acetylide to an ketone intermediate to give a proparglic alcohol.

Compared with the prior methods of preparation DPC 961, the process of this invention achieved with a chiral amino alcohol to mediate the addition reaction along an asymmetric pathway. The prior methods by a derivatization and fractional crystallization or 1, 4-diastereoselective addition protocol, both employing auxiliary(*Journal of Organic Chemistry* vol.68, no.3, **2003**, 754-761; *Tetrahedron Letter* vol.41, **2000**, 3015-3019). *WO* 200170707 disclosed a asymmetric processes for preparing DPC961 via chiral moderated asymmetric addition. However, in this process large excess strong base (lithium alkyl and LHMDS) and excess chiral ligand was used under very strict condition(-20°C), while the process of this invention can be performed with very mild reaction condition (20-40°C). The ligand used in the reaction is less expensive, futher more it can be recycled. The workup is also very simple. All of this will reduced the cost of the process greatly.

Further, it is unexpected that reaction of zinc or copper acetylide with a trifluoromethyl

ketimine produces an optically active product. The invention not only provide a kind of novel ligand in the enantioselective alkynylation of ketimine, but also provide a practical industrial process of preparation DPC 961. In the present invention, this is achieved with a chiral amino alcohol to mediate the addition reaction along an asymmetric pathway. The unusually high levels of optical activity (up to 99% ee) and very mild reaction condition make the method advantageous and practical.

Best Mode for Carrying Out the Invention

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

Example 1

Preparation of (1R, 2R)–2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane -1,3-diol:

See reference Jiang, B.; Chen, Z. L.; Tang, X. X. *Org. Lett.* **2002**, *4*, 3451.

Example 2

Preparation of (1R, 2R)–3-(*t*-butyloxy)-2-*N,N*-dimethylamino-1-(*p*-nitrophenyl) propane-1-ol: Concentrated H_2SO_4 (0.8g) was added dropwise to a solution of (1R, 2R)–2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol(1.8 g, 7.5 mmol) in CH_2Cl_2 (20 mL) at 0-5 °C. Isobutene gas was bubbled for 1h with the temperature maintained at 0-5 °C. Concentrated H_2SO_4 (0.2 g) was added dropwise, the mixture was allowed to warm to room temperature and was stirred vigorously for 5-7 hrs with the isobutene bubbling into. Then the mixture was cooled to 0-5°C and washed with K_2CO_3 (sat). The organic layer was dried with Na_2SO_4 and concentrated *in vaccuo*. Purified by flash chromatography on silica gel afforded the ligand (1.44 g, 65%). (Hexane: EtOAc = 1:1). mp 100.0 – 101.3 °C; $[\alpha]_D^{20}$ = +23.5 (c, 1.00, $CHCl_3$); FTIR (KBr) 3333, 2972, 1606, 1523,1357,1197,861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 4.59 (d, J = 9.9 Hz, 1H), 3.34 (dd, J = 3.0 Hz, and 9.9 Hz, 1H), 3.21 (dd, J = 6.5 Hz, and 10 Hz, 1H), 2.56 (m, 1H), 2.47 (s, 6H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 147.6,

128.46, 123.49, 73.3, 70.3, 69.8, 56.0, 41.8, 27.4; MS (EI) *m/e* 223(M+-73, 3), 209 (21), 144 (68), 88 (100), 71(10), 57(31); Anal. calcd. for $C_{15}H_{24}N_2O_4$: C, 60.81; H, 8.11; N, 9.46. Found: C, 60.72; H, 8.26; N, 9.14.

Example 3

Preparation of (1R, 2R)–3-(*t*-butyldimethylsilyloxy)-2-*N,N*-dimethylamino-1-(*p*-nitrophenyl)propane-1-ol:

(1R, 2R)–2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol (1.946 g, 8.1 mmol) was dissolved in CH_2Cl_2 (30 mL), TBDMSCl (1.28g, 5.3 mmol) and imidazole (1.4 g, 20.6 mmol) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 2.72 g proguct. FTIR (KBr) 3344, 2954, 1606, 1525,1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25-8.20 (d, J = 8.5 Hz, 2H), 7.6-7.55 (d, J = 8.5 Hz, 2H), 4.65 (d, J = 9.7 Hz, 1H), 3.77-3.6(dd, J = 11.3 Hz, 2.7 Hz 1H), 3.5-3.45(dd, J = 11.3 Hz, 6.0 Hz, 1H), 2.50 (m, 7H), 1.85 (s, 9H), 0.1 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 147.4, 128.0, 123.3, 69.0, 57.1, 41.6, 25.7, 17.9, -5.9; MS (EI) *m/e* 297(M+-57, 0.3), 209 (8.2), 202(100). Anal. calcd. for $C_{17}H_{30}N_2O_4Si$: C, 57.60; H, 8.53; N, 7.90. Found: C, 57.82; H, 8.18; N, 7.77.

Example 4

Preparation of (1R, 2R)–3-(triphenylmethoxy)-2-*N,N*-dimethylamino-1-(*p*-nitrophenyl) propane-1-ol:

(1R, 2R)–2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol(1.946 g, 8.1 mmol) was dissolved in CH_2Cl_2 (50 mL), Triphenylmethane chloride (TrCl) (3.34 g, 12 mmol) and Et_3N (2 mL) was added at 0°C. The mixture was stirred for overnight at rt. Work up to give 3.7 g proguct. FTIR (KBr) 3344, 2954, 1606, 1525,1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09-8.06 (d, J = 8.4 Hz, 2H), 7.36-7.33 (d, J = 8.6 Hz, 2H), 7.25-7.17 (m, 15H), 4.27 (d, J = 10.0 Hz, 1H), 3..28(dd, J = 10.2 Hz, 6.4 Hz, 1H), 3.01(dd, J = 10.7 Hz, 3.9 Hz, 1H), 2.71 (m, 1H), 2.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 147.6, 143.6, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 127.3, 123.7, 87.7, 70.9, 70.6, 58.6, 41.6.

Example 5

Preparation of (1R, 2R)–2-*N*-benzyl-2-*N*-methylamino-3-(*p*-nitrophenyl)propane-1, 3-diol:

(1R, 2R)-2-aminol-3-(*p*-nitrophenyl)propane-1,3-diol (2.12 g, 10 mmol) and benzaldehyde (1.2 g, 10.5 mmol) was added to methanol (10 mL), then $CuSO_4$ (0.2 g) was added to the mixture. The mixture was refluxed for 7 hr, cooled to rt and filtered. To the filtrate was added THF (10 mL). $NaBH_4$ (0.4 g) was added slowly. The resulting mixture was refluxed for 2 hr and cooled. 5% HCl was added to acidified the solution. Extracted with ether and concentrated. The residue mixture was refluxed with HCHO(10 mL) and HCOOH(10 mL) for 8hr. The mixture was cooled and nutralized with NaOH. Extracted with CH_2Cl_2 and dried with $NaSO_4$. After purification give 1.2 g product.

Example 6

Preparation of (1R, 2R)–3-(*t*-butyldimethylsilyloxy)- 2-*N*-benzyl-2-*N* -methylamino -1-(*p*-nitrophenyl) propane-1-ol

(1R, 2R)–2-*N*-benzyl-*N*-methylamino-3-(*p*-nitrophenyl)propane-1,3-diol (632 mg) was dissolved in CH_2Cl_2 (15 mL), TBDMSCl (300 mg, 2 mmol) and imidazole (136 mg, 2 mmol) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 600 mg proguct. FTIR (KBr) 3344, 2972, 1606, 1525,1348 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.38-7.31 (m, 5H), 4.70 (d, J = 9.6 Hz, 1H), 4.04 (d, J = 13.0 Hz, 1H), 3.77-3.55(m, 3H), 2.70 (m, 1H), 2.43 (s, 3H), 0.90 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 147.6, 138.46, 129.2, 128.8, 128.4, 127.7, 123.69, 70.3, 69.8, 60.1, 58.0, 37.5, 26.0, 18.3, -5.4; MS (EI) *m/e* 415(M+-15, 0.9), 278 (100), 91(73);

Example 7

Preparation of (1R, 2R)–3-(triphenylmethoxy)-2-*N*-benzyl-2-*N*-methylamino-1-(*p*-nitrophenyl) propane-1-ol:

(1R, 2R)–2-*N*-benzyl-*N*-methylamino-3-(*p*-nitrophenyl)propane-1,3-diol (380 mg, 1.2 mmol) was dissolved in CH_2Cl_2 (15 mL), TrCl (334 mg, 1.2 mmol) and Et_3N (0.2 mL) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 500 mg proguct. mp 58.0 – 59.3 °C; FTIR (KBr) 3314, 2926, 1602, 1521,1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.8 Hz, 2H), 7.40-7.19 (m, 22H), 4.30 (d, J = 9.6 Hz, 1H), 3.94 (d, J = 13.0 Hz, 1H), 3.73(d, J = 6.8 Hz, 1H), 3.36 (m, 1H), 3.06 (m, 1H) 2.89 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 147.6, 143.46, 138.2, 129.3, 128.8, 128.7, 128.6 ,128.4, 128.0, 127.7 127.4, 123.7, 87.8, 70.5, 69.8, 60.1, 58.0, 37.0; MS (EI) *m/e* 406(M+-152, 24.9), 243 (100);Anal. calcd. for $C_{15}H_{24}N_2O_4$: C, 77.42; H, 6.09; N, 5.02. Found: C, 77.26; H, 6.06; N, 4.65.

Example 8

Preparation of (1R, 2R)–3-(triphenylmethoxy)-2-*N,N*-dimethylamino-1-(phenyl) propane-1-ol:

(1R, 2R)–2-*N,N*-dimethylamino-3-(phenyl)propane-1,3-diol (1.95 g, 10 mmol) was dissolved in CH_2Cl_2 (50 mL), Triphenylmethane chloride (TrCl) (3.33 g, 12 mmol) and Et_3N (2 mL) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 4.0 g proguct. FTIR (KBr) 3344, 2954, 1609, 1525,1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.06 (m, 20H), 4.87 (d, J = 10.0 Hz, 1H), 3.76(dd, J = 10.2 Hz, 6.4 Hz 1H), 3.51(dd, J = 10.7 Hz, 3.9 Hz 2H), 2.80 (m, 1H), 2.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.9, 128-129(16 C), 125.7-126.6(4 C), 84.9, 72.9, 68.6, 69.6, 49.6, 39.6.

Example 9

Preparation of (1R, 2R)–3-(triphenylmethoxy)-2-*N,N*-dimethylamino-1-(*p*-methylsulphonylphenyl) propane-1-ol:

(1R, 2R)–2-*N,N*-dimethylamino-3-(*p*-methylsulphonylphenyl)propane-1,3-diol (5.46 g, 20 mmol) was dissolved in CH_2Cl_2 (80 mL), Triphenylmethane chloride (TrCl) (6.8 g, 25 mmol) and Et_3N (4 mL) was added at 0 °C. The mixture was stirred for overnight at rt. Work up to give 9.10 g proguct. FTIR (KBr) 3344, 2954, 1609, 1525,1349 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 7.48-7.40 (d, J = 8.4 Hz, 2H), 7.27-7.19 (d, J = 8.6 Hz, 2H), 7.12-7.04 (m, 15H), 4.86(d, J = 10.0 Hz, 1H), 3.72 (dd, J = 10.2 Hz, 6.4 Hz 1H), 3.56(dd, J = 10.2 Hz, 6.4 Hz 2H), 2.94(s, 3H), 2.81(m, 1H), 2.38(s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.0, 138.6, 135.0, 129-126(16C), 84.9, 72.9, 69.6, 68.0, 49.6, 41.0, 39.6.

Example 10

Preparation of (1R, 2R)–2-*N* -prrrolidinyl-3-(*p*-nitrophenyl)propane-1,3-diol:

(1R, 2R)–2-amino-3-(*p*-nitrophenyl)propane-1,3-diol (2.12 g, 10 mmol) dissolved in DMF (10 mL), anhydrous K_2CO_3 (3.15 g, 22 mmol) was added at 0-5 °C. 1,4-dibromobutane (2.4 g, 11 mmol) was added dropwise. The mixture was allowed to warm to room temperature and was stirred vigorously for 35 h. After filtration, the solution was added to water and extracted with EtOAc. Purified to give the product 2.2 g (83%) as an yellow oil. FTIR (neat) 3393, 2969, 1605, 1521, 1348cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.9 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 4.63 (d, J = 8.1 Hz, 1H), 3.80 (br, 2H), 3.56 (m, 2H), 2.81-2.70 (m, 5H), 1.79-1.68 (m, 4H); MS (ESI) *m/e* 267(M^++1).

Example 11

Preparation of (1R, 2R)–3-(*t*-butyldimethylsilyloxy)-2-*N*-prrrolidinyl-1-(*p*-nitro phenyl)propane-1-ol:

(1R, 2R)–2-*N* -prrrolidinyl-3-(*p*-nitrophenyl)propane-1,3-diol (2.66 g, 10 mmol) was dissolved in CH_2Cl_2 (80 mL). After cooled to 0-5 °C, imidazole (680 mg, 10 mmol) was added. TBDMSCl (1.65 g 11 mmol) was added in three portions. The mixture was allowed to warm to room temperature and was stirred for 5h. After workup to give 3.0 g (79%) yellow oil as product. FTIR (neat) 3346, 2937, 2924, 2858, 1604, 1525, 1347cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.9 Hz, 2H), 4.70 (d, J = 8.5 Hz, 1H), 3.65 (dd, J = 4.0 Hz, and 11.0 Hz, 1H), 3.52 (dd, J = 5.3 Hz, and 10.8 Hz, 1H), 2.82-2.71 (m, 5H), 1.83-1.73 (m, 4H), 0.85 (s, 9H), -0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 147.2, 127.7, 123.2, 69.8, 67.4, 58.2, 49.2, 25.7, 23.4, 17.9, -5.8; MS (ESI) *m/e* 381(M^++1).

Example 12

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butylpropane-1-ol (2.96 g, 0.2 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) and 4-chloro-2-trifluoroacetyl aniline(1.74 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (75% yield, 99.3% ee).

Example 13

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 25 °C for 2 hr. The 4-chloro-2-trifluoroacetyl aniline(2.23 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (60% yield, 90.1% ee).

Example 14

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butylpropane-1-ol (2.96 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) was added to

the mixture. The mixture was stirred at 25 °C for 2 hr. The 4-chloro-2-trifluoroacetyl aniline(2.23 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (60% yield, 99.1% ee).

Example 15

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (354 mg, 1 mmol) and $Zn(OTf)_2$ (0.36 g, 1 mmol) was dissolved in toluene (2 mL) at 25°C. NEt_3 (0.21 mL, 1.5 mmol) was added. After 1 hr, the neat *t*-butylacetylene (1.3 mL, 12 mmol) was added to the mixture. The 4-chloro-2-trifluoroacetyl aniline (2.3 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding 1N HCl aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (85% yield, 94.1%ee).

Example 16

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*-benzyl-*N*-methylamino-1-(4-nitrophenyl)-3-*O*-tritylpropane-1-ol (558 mg, 1 mmol) and $Cu(OTf)_2$ (0.36 g, 1 mmol) was dissolved in toluene (10 mL) at 25°C. NEt_3 (0.21 mL, 1.5 mmol) was added. After 1 hr, the neat phenylacetylene (1.1 mL, 12 mmol) was added to the mixture. The 4-chloro-2-trifluoroacetyl aniline (2.3 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was

collected by filtration, and dried to give the adduct product (67% yield, 55%ee).

Example 17

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-methyl-2-*N*-benzyl-*N*-methylamino-1-phenyl-ethane-1-ol (2.55 g, 10.0mmol) and $Zn(OTf)_2$ (3.6 g, 10.0mmol) was dissolved in toluene (10mL) at 25°C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 25 °C for 2 hr. The 4-chloro-2-trifluoroacetyl aniline (2.23 g, 10 mmol) was added in one port. The mixture was stirred at 25°C for 10hr. The resulting solution was quenched by adding NH_4Cl aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the adduct product (51% yield, 96.1% ee).

Example 18

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butylpropane-1-ol (2.96 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g,10 mmol) was dissolved in toluene (10 mL) at 25°C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 25 °C for 2 hr. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (95% yield, 99.3% ee).

Example 19

Preparation of the DPC961

The *p*-methoxybenzyl protected DPC 961 (2 mmol) was dissolved in 10% aqueous CH_3CN (10 mL), and ceric ammonium nitrate (4. 4g, 8 mmol) was added. After stirring for 4 hr at 25 °C, the reaction was diluted with water and extracted with EtOAc. The combined organic layer was concentrated *in vacuo* to afford DPC 961 in 80% yield.

Example 20

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g,10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) was added to the mixture. The p-methoxybenzyl protected ketimine (3.69 g,10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (72% yield, 99.1% ee).

Example 21

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-triphenylmethylpropane-1-ol (4.82 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2mL, 12mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69g,10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and

concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (76% yield, 98.0% ee).

Example 22

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*-methyl-*N*-benzyl -1-(4-nitrophenyl)-3-*O*-triphenylmethylpropane-1-ol (5.58 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene(10 mL) at 25°C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine(3.69 g,10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (80% yield, 51.0%ee).

Example 23

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*-methyl-*N*-benzyl-1-(4-nitrophenyl)-3-*O*-triphenylmethylpropane-1-ol (5.58 g, 10 mmol) and $Cu(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (68% yield, 98.0% ee).

Example 24

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (354 mg, 1 mmol) and $Zn(OTf)_2$ (0.36 g, 1 mmol) was dissolved in toluene (10 mL) at 25°C. NEt_3 (0.21 mL, 1.5 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g,10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (75% yield, 98.1% ee).

Example 25

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*-methyl-*N*-benzyl-1-(4-nitrophenyl)-3-*O*-triphenylmethylpropane-1-ol (558 mg, 1 mmol) and $Cu(OTf)_2$ (0.36 g, 1 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (0.21 mL, 1.5 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g,10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (67% yield, 45% ee).

Example 26

Addition of *t*-butylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-

(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25°C. $HNiPr_2$ (2.0 mL) was added. After 1 hr, the neat *t*-butylacetylene(1.3 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g,10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (45% yield, 96.5% ee).

Example 27

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 kg, 10 mol) and $Zn(OTf)_2$ (3.6 kg, 10 mol) was dissolved in toluene (10 L) at 25 °C. NEt_3 (2.0 L, 15 mol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 L, 12 mol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 kg,10 mol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (90.9% yield, 99.1% ee).

Example 28

Addition of phenylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1 -(4-nitrophenyl)-3-*O*-*t*-butylpropane-1-ol (2.96 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g,10 mmol) was dissolved in THF (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat phenylacetylene (1.1 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl

protected ketimine (3.69 g,10 mmol) was added in one port. The mixture was stirred at 25°C for 10hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (91% yield, 99.0%ee).

Example 29

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethyl-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene (1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 50°C for 2 hr and then cooled to 25 °C. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (81% yield, 97.1% ee).

Example 30

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethylamino-1-(4-nitrophenyl)-3-*O*-*t*-butyldimethylsilylpropane-1-ol (3.54 g, 10 mmol) and $ZnBr_2$ (2.3 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) was added to the mixture. The mixture was stirred at 50 °C for 2 hr and then cooled to 25 °C. The *p*-methoxybenzyl protected ketimine (3.69 g,10 mmol) was added in one port. The mixture was stirred at 25

°C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (31% yield, 63.1%ee).

Example 31

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethylamino-1-(4-nitrophenyl)-2-*t*-butyloxycarbonyl-ethane-1-ol (3.1 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (95% yield, 99.3% ee).

Example 32

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethylamino-1-(4-nitrophenyl)-2-hydroxycarbonyl-ethane-1-ol (2.5 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo.* Heptane was added to the mixture slowly. The white solid was

collected by filtration, and dried to give the product (95% yield, 90.3% ee).

Example 33

Addition of cyclopropylacetylene to the ketimine

Under argon atmosphere, the amino alcohol ligand (1R, 2R)-2-*N*,*N*-dimethylamino-1-(4-nitrophenyl)-2-methyl-ethane-1-ol (2.3 g, 10 mmol) and $Zn(OTf)_2$ (3.6 g, 10 mmol) was dissolved in toluene (10 mL) at 25 °C. NEt_3 (2.1 mL, 15 mmol) was added. After 1 hr, the neat cyclopropylacetylene(1.2 mL, 12 mmol) was added to the mixture. The *p*-methoxybenzyl protected ketimine (3.69 g, 10 mmol) was added in one port. The mixture was stirred at 25 °C for 10 hr. The resulting solution was quenched by adding saturated citric acid aqueous solution. The mixture was extracted with EtOAc. The aqueous was saved for the recovery of ligand. The combined organic layers was dried with Na_2SO_4 and concentrated *in vacuo*. Heptane was added to the mixture slowly. The white solid was collected by filtration, and dried to give the product (95% yield, 60.5% ee).